REMARKS/ARGUMENTS

In response to the Office Action of March 7, 2005, Applicants provide the following remarks, which further support patentability of the present application. Favorable consideration of all pending claims is earnestly solicited.

Claims 11-28 have been rejected under 35 U.S.C.§ 112, first paragraph, as allegedly directed to non-enabled subject matter. It is the position of the Examiner that while the specification is enabling for *treating* neointimal proliferation and thickening and/or restenosis and /or vascular occlusion following vascular injury or manifestations of chronic rejection in a recipient of organ or tissue transplant or acute or chronic rejection in a recipient of organ or tissue xenograft transplant with the administration of 40-O-(2-hydroxy0ethyl-rapamycin, it is not enabling for *preventing* these same conditions with the administratin of 40-O-(2-hydroxy)ethyl-rapamycin and a second agent disclosed in claims 11 and 20. March 2, 2005, Office Action, pages 2-3.

The Examiner then cites five of the eight factors relevant in assessing if a disclosure would have required undue experimentation under *In re Wands*, 8 USPQ2d 1400 (CAFC 1988). On page 4 of the Office Action, under the Wands factors "the nature of the invention, state of the prior art, relative skill of those in the art and the unpredictability of the art", the Examiner has indicated that "there are no known preventive therapies for neointimal proliferation and thickening and/or restenosis and /or vascular occlusion following vascular injury or manifestations of chronic rejection in a recipient or organ or tissue xenograft transplant." Office Action, page 4.

Applicants respectfully traverse the rejection for the following reasons. Page 7 of the application provides data which indicates that animals undergoing kidney transplant and administered 40-O-(2-hydroxy)ethyl-rapamycin (compound A) have significantly lower MRI score of rejection, histologic score for cellular rejection and vessel changes and a significantly lower reduction in perfusion rate assessed by MRI than animals of the placebo group. Pages 8-9 of the specification demonstrate that compound A significantly inhibits graft infiltration and neointima

formation in animals receiving an aorta transplant. Pages 9-10 of the specification demonstrate that in animals undergoing balloon angioplasty, intimal thickening is significantly less in vessels of rats receiving compound A starting as early as three days prior to balloon injury, compared to control animals. Pages 10-11 provide results for animals undergoing heart xenotransplantation, where compound A results in prolonged survival in both athymic and euthymic recipients.

In spite of the teachings and data supporting such teachings provided by the specification discussed above, the Examiner has stated that even for the data presented, no direction is provided to prevent the conditions and their causes. Office Action, page 6. Applicants respectfully submit that the present application is directed to preventing and treating certain conditions and manifestations of such conditions. Thus, none of claims 11-28 is directed to prevention of the *causes* for the conditions recited therein. Applicants respectfully submit that the Examiner has applied a hyper-technical meaning to the term "prevention" as it is used in the specification and claims of the present invention. As taught by the specification of the present application, the presently claimed methods are useful in "preventing or treating" various conditions following a known, clinical event. For example, claims 20-28 are directed to preventing or treating neointimal proliferation and thickening and/or restenosis and/or vascular occlusion following vascular injury." Since it is predictable that neointimal proliferation and thickening and/or restenosis and/or vascular occlusion will occur following vascular injury (*see* specification, page 4, paragraphs 3 and 5, as well as the literature extant as of the effective filing date of the present application), one skilled in the art would reasonably understand that neointimal proliferation and thickening and/or restenosis and/or vascular occlusion following vascular injury should be *prevented*, and that administration of the compositions of the present invention should not be delayed until the onset of symptoms.

Claims 11-19 are also directed to preventing or treating manifestations of chronic rejection in a recipient of organ or tissue transplant or acute or chronic rejection in a recipient of organ or tissue xenograft transplant. Since it is predictable that chronic rejection will occur in a recipient of organ or tissue transplant and that acute or chronic rejection will occur in a recipient of organ or tissue xenograft transplant (*see* specification, page 4, paragraphs 1, 2 and 4, as well as the literature

extant as of the effective filing date of the present application), one skilled in the art would reasonably understand that these types of rejection following organ or tissue transplantation should be *prevented*, and that administration of the compositions of the present invention should not be delayed until the onset of symptoms.

That is, the compositions of the present invention would be administered earlier, rather than later in order to prevent chronic or acute rejection.

Further, the specification clearly teaches at page 12 that the compounds of formula I (which would include compound A) may be administered with other drugs in immunomodulating regimens. Such other drugs listed therein are recited in claims 11-28.

Thus, contrary to what the Examiner has asserted, there is ample guidance in the specification to enable one skilled in the art to practice the presently claimed invention, without having to engage in undue experimentation. Withdrawal of the rejection of claims 11-28 under the enablement provision of 35 U.S.C. §112, first paragraph, is therefore respectfully requested.

Claims 11-28 have also been rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over Cottens et al. (U.S. Patent No. 5,665,772) in view of Morris et al. (U.S. Patent No. 5,516,781).

Cottens et al. discloses certain methods such as treating or preventing organ or tissue transplant rejection. Cottens et al. is silent as to the therapeutic method of Applicant's claims, i.e., a method for preventing or treating neointimal proliferation and thickening and/or restenosis and/or vascular occlusion following surgery, or manifestation of chronic rejection or rejection in a xenograft transplant recipient.

Morris et al. teaches rapamycin but is silent as to 40-O-(2-hydroxy)ethyl-rapamycin.

As is well settled, a small modification in the structure of a molecule may completely change its biological properties. Rapamycin is a large macrolide molecule comprising a number of possible substitution/modification sites. Submitted herewith as Exhibit 1 is a paper by Sedrani et al. (*Transplantation Proceedings*, 30, 2192-2194 (1998)) which shows that a small change in the structure of rapamycin results in a dramatic change in biological activity. In particular, a substitution of a methyl or phenyl group for a hydrogen atom can result in loss of immunosuppressive activity.

This is shown in Sedrani et al for compound 3 (28-O-methyl-rapamycin) as compared with compound 1(the parent compound, rapamycin) wherein compound 3 had a 1000-fold loss of activity in the mixed lymphocyte reaction. Similarly, Sedrani et al. also shows loss of activity compound 6 (40-O-phenyl-rapamycin). Thus, one skilled in the art reading Sedrani et al. could not predict the effectiveness in a given method of rapamycin derivatives with simply one methyl or phenyl substitution.

Submitted herewith as Exhibit 2 is an article concerning chronic graft rejection by Fellstrom, C. and Larsson, E. (Immunological Reviews, No. 134, 83-98 (1993). The Fellstrom and Larson article indicates that chronic rejection is one of the major threats to graft function on a long term basis of transplanted hearts and kidneys. "It is characterized by a proliferative remolding of the graft vessels, along with structural changes of the parenchyma and gradual deterioration of the graft function. The pathogenesis is complex and multifunctional. There is no established means of prevention or treatment of chronic rejection" (page 94). The ability of known immunosuppressants to treat chronic rejection is unpredictable. This essential unpredictability is demonstrated by the fact that "the commonly used immunosuppressive agents such as cyclosporine A and prednisolone may also have a proatherologic potential. Cyclosporine A has been shown to have direct toxic effects on vascular endothelial and smooth muscle cells and steroids may indirectly have a detrimental effect because of induction of hyperlipidemia and increased peripheral insulin resistance" (page 91). Thus, in view of the Fellstrom and Larsson article, it is clear that certain of the known immunosuppressants currently used in allotransplantation, such as cyclosporin A, do not exhibit activity in the prevention or treatment of neointimal proliferation and thickening.

The rapamycin derivative of the present claims has a hydroxyethyl substitution, i.e., it has a primary OH function in position 40. It was not predictable, *a priori,* that 40-O-(2-hydroxyethyl)-rapamycin, even though it was known as having immunosuppressive properties as disclosed in Morris et al., would be active in the inhibition of neointimal proliferation and thickening, e.g., in preventing chronic graft rejection or restenosis.

With respect to the proliferative disorders taught in Morris et al., they are related to tumors or hyperproliferative skin disorders. There is no suggestion or any incentive in this reference to use 40-O-(2-hydroxyethyl)-rapamycin in the inhibition of proliferative vascular disorders (neointimal proliferation and thickening). Withdrawal of the rejection of claims 11-28 under 35 U.S.C.§ 103(a) is is therefore respectfully requested.

In view of the foregoing remarks, it is firmly believed that the subject case is in condition for allowance, which action is earnestly solicited.

Respectfully submitted,

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